ENHANCEMENT OF MIXING BY DROPLET-BASED MICROFLUIDICS

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ABSTRACT

Enhancement of mixing using electrowetting-on-dielectric (EWOD) actuation is demonstrated. Exponential improvement over simple diffusion is theorized, based on convolutions generated by discrete droplet flow. The relationship between particle size, distance diffused, and diffusion time is studied. An improvement of 50 times over simple diffusion is experimentally shown, using a simple dye-mixing experiment.

INTRODUCTION

Mixing is a serious problem in microfluidics, dominated by laminar flows of low Reynolds Number (Re). While there are efforts to enhance mixing for the usual continuous flows in microchannels [1-4], the new droplet-based microfluidics [5] presents us with an opportunity to greatly enhance mixing with ease. With the ability to digitize liquids into numerous droplets [6], one can enhance mixing by first digitizing two different liquids, mating the droplets in one-to-one fashion in parallel, and merging the mixed droplets into continuous flow, if necessary. We report a scheme for further enhancement *within* each droplet, so the mixing is enhanced in a most generalized fashion. We present the concept and experimentally verify it with the simplest example of mixing a deionized water (DI) droplet with a dyed droplet. The two droplets are first merged into one and driven along a loop designed for the mixing. Although this mixing scheme is valid for any droplet type flows, we demonstrate the concept by driving the droplets by electrowetting actuation. The experiment verifies mixing time is substantially lowered by driving along the mixing loop, an improvement over simple diffusion of two joined droplets.

CONCEPT

EWOD geometry:
The EWOD device utilizes a droplet squeezed between parallel plates. Its sides are not in contact with a solid surface. This is very important. It means that the sides of the droplet are free to move during "flow." The classic enclosed flow, however, is contacted on the sides, imposing a no-slip restriction to them. Furthermore, in an EWOD flow, the surface is pulling the droplet forward; while in a classic pressure-driven flow, the fluid is pushed from the center. These two geometries present radically different flows, as shown in Fig. 1. This figure is greatly simplified. The actual flow is three-dimensional in
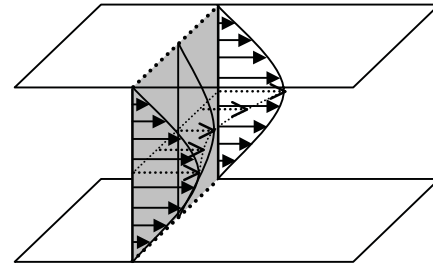
Flow A (open channel - EWOD)
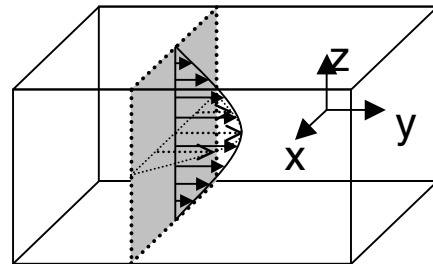
Flow B (closed channel - classic)

Fig. 1: Two flow fields.

nature, and vorticity cannot be neglected. However, the flows presented are sufficient to illustrate the inherent differences between the two geometries. Flow A is the parallel plate flow, and it is represented such that the z+ and z- planes are liquid-solid interfaces, while the x+ and x- planes are liquid-vapor interfaces. In flow B (classic channel flow), planes z+, z-, x+, and x- are all liquid-solid interfaces. In both flows, the y+ and y- planes are not interfaces in this illustration, and they can be assumed to be continuous. The gray plane is not a surface interface in either flow and is used for visual reference only. Velocity curves parallel to the Z planes are shown as dotted lines, while velocity curves parallel to the X planes are shown as solid lines. As can be seen, the lack of side walls, combined with the surface-driven flow creates quite a different velocity profile. This profile, combined with the circular geometry of a discrete droplet enhances mixing tremendously.

Mixing Enhancement:
The concept of our mixing enhancement is described in Fig. 2. Two droplets of different content are first joined into one. By driving the joint droplet towards the right, the interface between the two liquids is distorted and stretched by the velocity gradient in the liquid. Fig. 2 is our expectation of how a droplet will tend to circulate
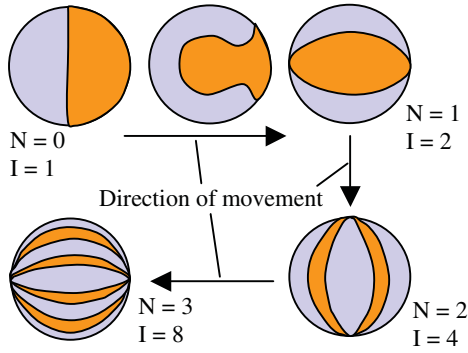
Fig. 2: Mixing pattern by rolling.
Viewed from above.

with movement and "roll" to form new layers of materials. A roll is one complete fold of the droplet layers, as shown in Fig. 2. By repeated change of rolling direction, the number of layers would increase exponentially, resulting in dramatically increased interface area between the two materials. In an idealized situation (i.e., perfect rolling and no diffusion), the number of layer interfaces I increase exponentially with the number of rolls N:

$$I = 2^N. \tag{1}$$

Reversibility:
For very low Re flows, fluid motions are reversible. To counteract this phenomenon, we designed our droplet to move along a circular path. For comparison, we reversed the movement on a linear stretch of electrodes, but were unable to demonstrate the reversibility because the flow had still a relatively high Re of 33. But, for smaller scale flows at lower speeds (e.g. Re < 1), we anticipate fluid reversibility effects and the effectiveness of our mixing loop to counteract the reversibility problem.

ANALYSIS

Diffusion time can be generally estimated to follow the relation [7]:

$$t = \frac{x^2}{2D} \tag{2}$$

for a three-dimensional point-source diffusion. D is the diffusion coefficient and x is the displacement. Diffusion time is proportionate to the square of the displacement, so smaller distances require exponentially smaller diffusion times. This means diffusion works well on the small scale, provided the diffusion coefficient doesn't become too large. However, the diffusion coefficient can be estimated from the Einstein relation:

$$D = \frac{kT}{F_s} \tag{3}$$

where k is Boltzmann's constant, T is absolute temperature, and F_s is Stokes' force (drag force on the small scale). Stokes' force has only been solved for spherical particles, so we'll use them for this analysis. It is generally believed that a sphere has the smallest Stokes drag for a particle of a certain volume. Stokes' solution for a sphere is

$$F_s = 3\pi\mu d \tag{4}$$

where d is the radius of the sphere and μ is the absolute viscosity of the surrounding medium. So, combining equations (2-4), we get:

$$t = \frac{3\pi x^2 \mu d}{2kT} \tag{5}$$

which shows the diffusion time for spherical particles from a point-source. Notice that time is directly proportional to particle radius. As seen in Table I, below, diffusion works best for mixing atomic particles at small distances. For biomolecules at larger distances (sample volumes), however, diffusion becomes inadequate for effective mixing.

Table I: First-passage diffusion times for spherical particles in room temperature water.

Diffusion Length (μm)	Potassium Ion (0.2 nm)	Globular Protein (6 nm)	HIV (100 nm)	Red Blood Cell (7 μm)
1	0.2 ms	6 ms	100 ms	7 s
10	20 ms	600 ms	10 s	700 s
100	2 s	60 s	20 min	20 hr
1000	200 s	100 min	30 hr	80 days

For many particles of importance, it is imperative that the diffusion length be reduced. Such length can be reduced exponentially through our mixing method. Creating lots of layers in a discrete droplet will naturally reduce the layer thickness, and since they are created exponentially, they become exponentially thinner. This improvement in time is shown by the plot in Fig. 3.
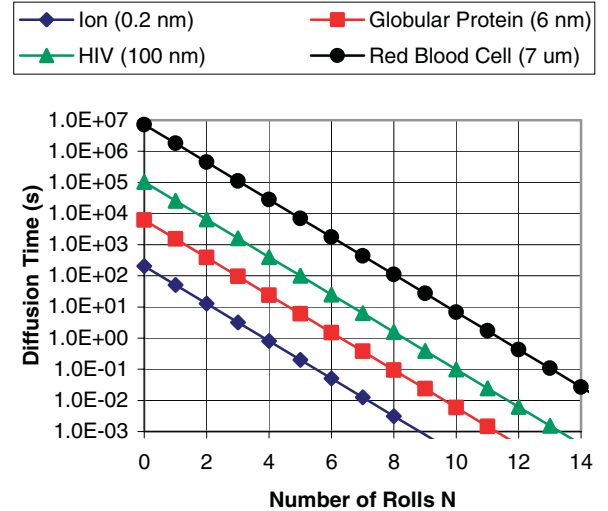

Fig. 3: Diffusion time as a function of number of Rolls N.

This plot is for an original diffusion length of 1000 μm in water at room temperature. The sizes of the particles are their spherical diameter. As can be seen, the diffusion time for large particles, such as red blood cells, is

significantly improved by only a few rolls. For example, reducing the diffusion time of a red blood cell from 10^7 seconds (100 days) to less than 1 second would take only 12 rolls.
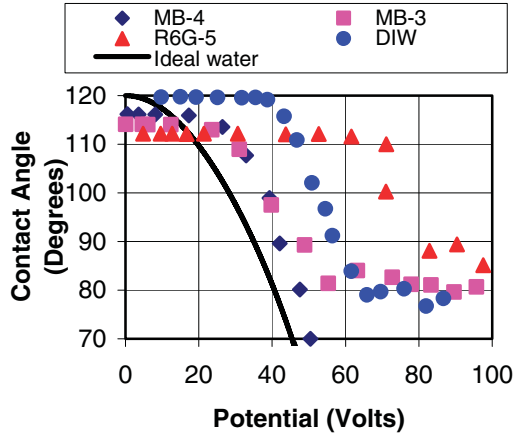
EXPERIMENT

Fig. 4: Contact angle changes of various dyes under EWOD.

Since we drive the droplets with electrowetting-on-dielectric (EWOD) for our mixing experiment, we evaluated several dyes for EWOD (Fig. 4). These dyes are 0.001M Mordant Blue 9 (MB-3), 0.0001M Mordant Blue 9 (MB-4), and 0.00001M Rhodamine 6G (R6G-5). De-ionized water is shown both with measurements and

(a) Cr/Au patterning (100/1000 Å)

(b) PECVD Oxide (1000 Å), wet etching (BOE)

(c) Teflon 0.25 μm

(d) Top glass: ITO (200 Å), Teflon (500 Å), Spacer (1.3 mm)

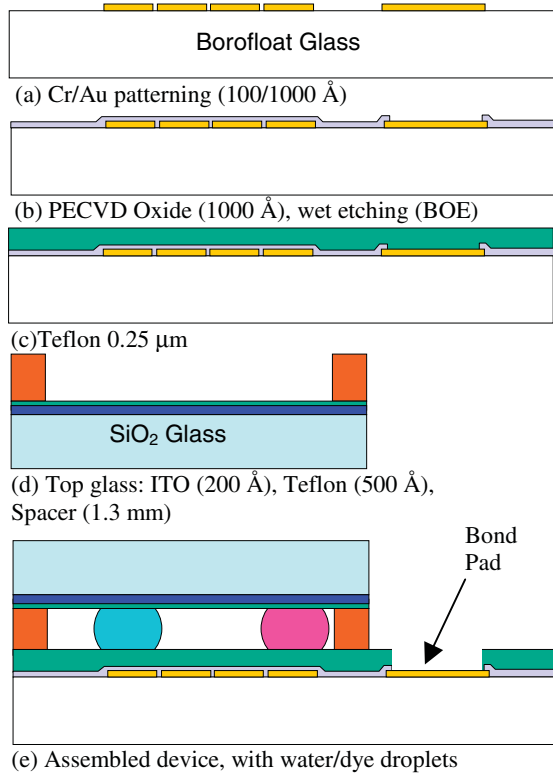(e) Assembled device, with water/dye droplets

Fig. 5: Fabrication process for mixing device.

using the Lippmann-Young equation (Ideal). The 0.0001M Mordant Blue 9 (MB-3) was chosen for its performance parity with DI water.

Fabrication process:
Fig. 5 shows the fabrication process for the device. (a) The first step is to evaporate 100 Å chromium and 1000 Å gold, which is patterned with AZ 5214 negative photoresist and wet etchants. (b) The second step is to coat the wafer with 1000 Å PECVD oxide, which is then patterned with AZ 5214 negative photoresist and BOE, to open the wire bonding pads. (c) The third step is to spin coat 2% AF 1600 Teflon®, which makes a layer 2500 Å thick. Teflon® is difficult to pattern without affecting its surface, so we are currently opening the bond pads by scraping, for convenience. (d) Concurrently, we produce the top glass using a polished float glass slide, coated with 2500 Å indium-tin-oxide (ITO), which is transparent and conductive. The cover glass is then coated with 0.6% AF 1600 Teflon®, which makes a layer 500 Å thick. The spacer is then attached to the cover glass. The cover glass is suspended above the substrate by an in-house built spacer. Since the cover glass has no features to speak of, it may be aligned by eye.

RESULTS & DISCUSSION

(a) Starting View, showing positions of figures and direction of movement

(b) t = 2/30 s   (c) t = 8/30 s   (d) t = 11/30 s   (e) t = 36/30 s
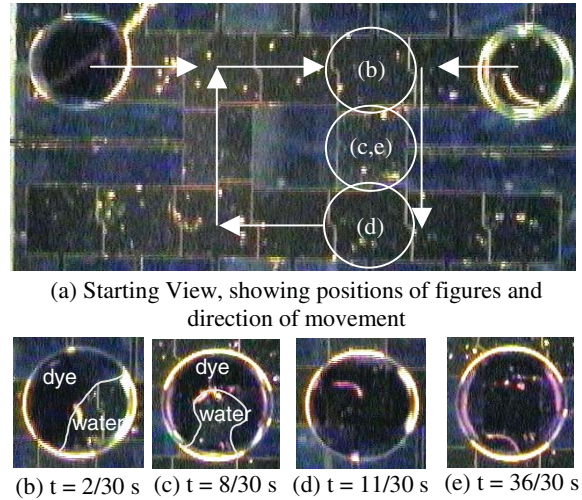
Fig. 6: A mixing experiment. Droplet movement shown on (a).

Fig. 6 shows a mixing experiment. The two droplets in Fig. 6(a) are combined at the electrode in Fig. 6(b), and the new droplet travels around the square loop of nine electrodes (Fig. 6(a)) in a clockwise direction. Figs. 6(b) and (c) verify the concept shown in Fig. 2 is closely matched in reality. Mixing appears complete after 1.2 seconds with a total travel of 9 mm (i.e., 4 rolls or 1 trip around the loop) after the droplets combine. The movement was accomplished with an actuation voltage of 30 V_{RMS} at a frequency of 1.0 kHz. The electrodes were actuated for 0.1 seconds at a time. By comparison, a droplet simply combined and not moved took 60 seconds
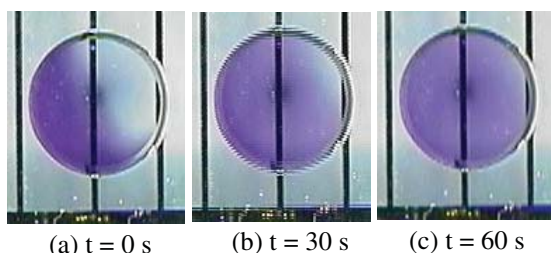
(a) t = 0 s   (b) t = 30 s   (c) t = 60 s

Fig. 7: Stationary mixing (by diffusion).

to achieve near complete mixing (Fig. 7). This simple scheme of letting the droplet travel along the loop speeded up the mixing by 50 folds. Because the mixing is enhanced exponentially with the number of rolls, larger particles can be mixed almost as fast.

CONCLUSION

We have shown that simple diffusion is inadequate for mixing large particles, such as biomolecules, and presented a simple method for enhancing their mixture. We performed a basic experiment to demonstrate our concept, with a resultant 50 fold increase in mixing capability. We also provided theory that indicated an exponential improvement in mixing, making larger particles equally mixable. When EWOD is used for actuation, this mixing loop costs little extra power consumption, little additional area, and no added complication in fabrication, while providing a solution for mixing large particles in microscale.

ACKNOWLEDGEMENTS

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